Journal of Molecular Structure 1224 (2021) 129209

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Substituent effects in the formation of a few acenaphthenone-2-ylidene ketones and their molecular docking studies and in silico ADME profile

Daly Kuriakose[#], Roshini K. Thumpakara[#], Jesna A, Jomon P. Jacob[*]

Department of Applied Chemistry, Cochin University of Science and Technology, Kochi-682 022, Kerala, India

ARTICLE INFO

Article history:
Received 24 July 2020
Revised 3 September 2020
Accepted 4 September 2020
Available online 4 September 2020

Keywords:
Claisen-Schimdt reaction
Aldol condensation
acenaphthenequinone
Acetophenone
Acenaphthenone-2-ylidene ketones
Molecular docking

ABSTRACT

We observed intriguing substituent effects in the reaction between 4-substituted acetophenones and acenaphthenequinone in the presence of KOH in methanol. In all cases, expected Claisen-Schimdt condensation was the first step. However, depending on the nature of 4-substituent on acetophenone, the initially formed condensation product remain unchanged or underwent Domino sequence of reactions to give three different 2:2 adducts arising through three distinct pathways. The interactions of acenaphthenone-2-ylidene ketones with the target proteins were performed by molecular docking studies. The prediction of in silico ADME belongings of the synthesized compounds revealed substantial drug-likeness characters based on Lipinski's rules.

1. Introduction

Claisen-Schimdt reaction, also called crossed-aldol condensation, is the condensation between aldehydes/ketones and carbonyl compounds leading to the formation of β-hydroxycarbonyl compounds which undergo subsequent dehydration to form α,β- unsaturated carbonyl compounds. This reaction is generally catalysed by acids or bases under room temperature or conventional heating [1,2] or microwave irradiation [3]. To avoid by-products and increase the yield of the products several protocols are developed using different catalysts [4–8]. β-Hydroxycarbonyl compounds have played a major role in synthetic organic chemistry [9–11] and α,β-unsaturated carbonyl compounds are widely used in pharma industries [12–15].

Acetophenone undergoes base catalysed Aldol condensation with benzil to form α,β-unsaturated ketone as the stable end product [16]. Based in this observation, we examined the Claisen-Schimdt reaction between acetophenone (**2a**) and acenaphthenequinone (**1**) in methanol in the presence of KOH [17,18]. Interestingly, we obtained three complex molecules by Michael-aldol domino reaction sequence. These 2:2 domino products (**4a, 5a, 6a**) were formed from a common Claisen-Schmidt condensed product **3a** [17] and the detailed mechanism of the above reaction was established in our recent publication (Scheme 1) [18]. Even after repeated attempts we could neither isolate nor detect (GC-MS, LC-MS) the 1:1 adduct **3a**. However, we could successfully generate **3a** by alternative routes (*vide infra*).

Molecular docking studies were exploited to show the possible binding mode of the test molecule with its target protein aiming to explain its anticancer activity [19–21]. To study the drug like character of synthesised acenaphthenone-2-ylidene ketones (**3a-f**), we have explained with the help of Swiss ADME software.

2. Results and Discussion

We have repeated the Claisen-Schmidt reaction of acenaphthenequinone (**1**) with acetophenones having different substituents at the 4-position (**2b-f**) to study the generality of the reaction. We observed dramatic substituent dependence in these reactions. While 4-chloro and 4-methylacetophenone reacted with acenapthenequinone to give three 2:2 adducts (**4b, 4c** - **5b, 5c** - **6b, 6c**) as described earlier [18], other acetophenone derivatives behaved differently, 4-bromo, 4-methoxy and 4-phenyl substituted acetophenones gave the expected 1:1 adduct, **3d-f** as the only product (Scheme 1). The 2:2 adducts formed were separated

* Corresponding author.
E-mail address: jacobpjomon@yahoo.com (J.P. Jacob).
# These two authors contributed equally.

https://doi.org/10.1016/j.molstruc.2020.129209
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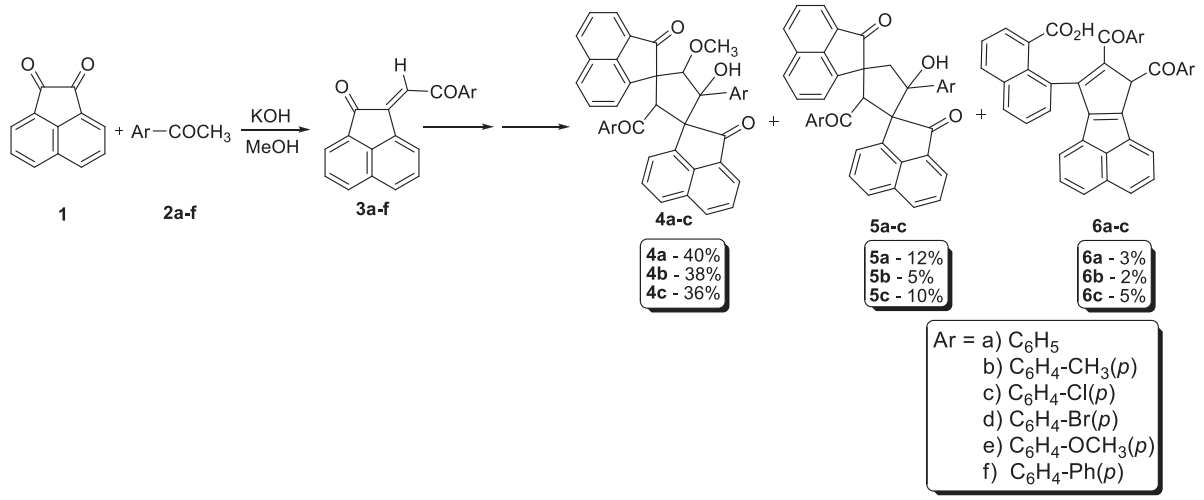
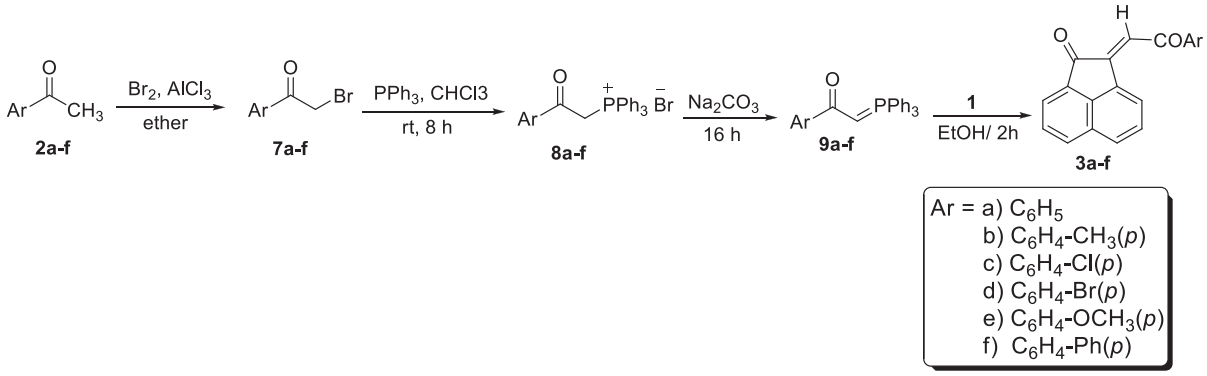


Scheme 1. Reaction between acenaphthenequinone (**1**) and acetophenones (**2a-f**).



Scheme 2. Wittig route for the synthesis of acenaphthenone-2-ylidene ketones (**3a-f**).

by column chromatography and purified by recrystallization. The compounds were characterised by ^{1}H, ^{13}C NMR and SCXRD [18,22,23] analyses. Inductive, mesomeric and steric factors could not satisfactorily account for the dichotomous reaction sequence of acetophenone-acenaphthenequinone reaction.

Our further investigations to unravel the mechanism of the reaction pointed towards a remarkable substituent effect in controlling the reactivity of acenaphthenone-2-ylidene ketones (**3a-f**). We have independently synthesised the intermediate acenaphthenone-2-ylidene ketones **3a-f** by adopting the Wittig route (Scheme 2). ln this reaction sequence, phenacyl bromides **7a-f** were first synthesised by the bromination of various para-substituted acetophenones **2a-f** using diethyl ether as solvent in the presence of anhydrous aluminium chloride. Phenacyl bromide derivatives **7a-f** were converted to corresponding phenacyltriphenylphosphonium bromides **8a-f** by the reaction with triphenylphosphine. In the presence of sodium carbonate, corresponding ylides **9a-f** were formed and they reacted with acenaphthenequinone (**1**) to form required acenaphthenone-2-ylidene ketones **3a-f**.

Independently synthesised acenaphthenone-2-ylidene ketones **3a-c** were treated with KOH in methanol. While **3d-f** remained unchanged even after refluxing for 12 h, **3a-c** underwent further transformation to give the 2:2 adducts **4a-c** within 4 h. This observation supports the reaction sequence depicted in Scheme 1 indicating further transformations of **3** to give **4** and presumably, **5** and **6** attesting the role of remote substituents in the reactivity of acenaphthenone-2-ylidene ketones **3a-f**.

Diversity of the above reaction may depend on the geometry or electronic factors of acenaphthenone-2-ylidene ketones (**3a-f**) having different substituents. To study the effect of geometry, we have computationally optimized the geometry of acenaphthenone-2-ylidene ketones (**3a-f**) using the software Gaussian (Table 1).

Based on optimized structures collected in Table 1, it is clear that acenaphthenone-2-ylidene ketones **3a-f** have similar geometry and hence geometry is not a significant factor in controlling the reactivity of **3**. So the difference in reactivity of **3a-f** may be due to electromeric effects induced by substituents at the *para* position of the benzoyl group in the 1:1 adducts, **3a-f**. A clear correlation is elusive since both electron withdrawing (Cl) and electron releasing (CH_3) substituents assist 2:2 adduct formation while both Br and -OMe substituents rendered the initially formed 1:1 adducts unreactive towards further transformations under the conditions employed by us.

3. Molecular docking

The AutoDock is an automatic docking programme designed for the prediction of the binding among small molecules forexample drug candidates and the receptor having known 3D structure [24–30]. Molecular docking studies were performed using AutoDock 4.2 Vina software to confirm the anticancer activity of acenaphthenone-2-ylidene ketones (3a-f) against different proteins *viz* **4I4T, 4I55, 4YJ2** and **4YJ3**. Crystal structure of the target proteins were downloaded from the RSCB PDB website in the PDB

Table 1
Energy minimized structures of acenaphthenone-2-ylidene ketones (**3a-f**) using Gaussian.

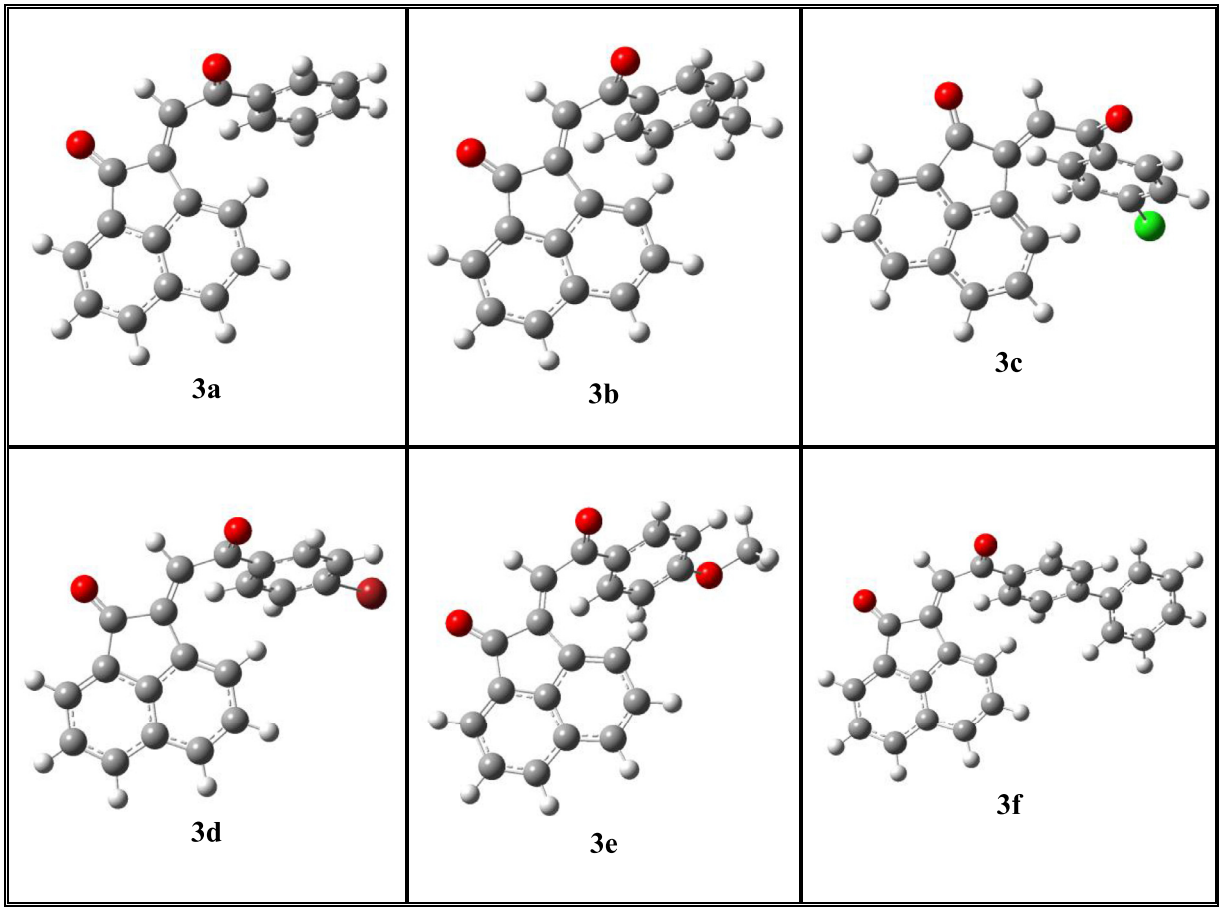


Table 2
All interacting residues between acenaphthenone-2-ylidene ketones and selected target proteins.

Proteins	Molecules	All interacting residues
4I4T	**3a**	ARG F: 44, PHE F: 49, ARG F: 66, ALA F: 68, ASP F: 69, ALA F: 335.
	3b	VAL F: 13, ALA F: 68, LEU F: 314, ALA F: 335, PRO F: 336.
	3c	PHE F: 49, ALA F: 68, ASP F: 69, ARG F: 73
	3d	ARG F: 44, ARG F: 46, PHE F: 49, ARG F: 66, ALA F:68, ASP F: 69, ALA F: 335.
	3e	ARG F: 44, LEU F: 47, PHE F: 49, ARG F: 66, ALA F: 68, ASP F: 69, ALA F: 335.
	3f	ARG F: 44, ARG F: 46, PHE F: 49, ARG F: 66, ALA F: 68, ASP F: 69, ALA F: 335.
4I55	**3a**	GLY B: 10, CYS B: 12, GLU B: 71, ALA B: 99, ASN B: 101, THR B: 145, GLY B: 146, ASP B: 179.
	3b	GLN B: 11, CYS B: 12, GLU B: 71, ASN B: 101, GLY B: 144, VAL B: 171, PRO B: 173.
	3c	VAL B: 177, ASP B: 179, TYR B: 224, LEU B: 227, VAL C: 250, VAL C: 353.
	3d	CYS B: 12, SER B: 140, VAL B: 171, MET B: 172, PRO B 173.
	3e	GLN B: 11, CYS B: 12, GLU B: 71, ALA B: 99, ASN B: 101, GLY B: 144, VAL B: 177, ASP B: 179.
	3f	TYR B: 224, LEU C: 248, PRO C: 325, VAL C: 353.
4YJ2	**3a**	VAL B: 177, SER B: 178, LEU C: 248, PRO C: 325, VAL C: 353, ILE C: 355.
	3b	VAL B: 177, SER B: 178, TYR B: 224, LEU B: 227, LEU C: 248, PRO C: 325, VAL C: 353, ILE C: 355.
	3c	VAL B:177, TYR B: 224, LEU C:248, PRO C: 325, VAL C: 353, ILE C: 355.
	3d	LYS B: 105, LYS C: 163.
	3e	CYS B: 12, GLN B: 15, GLU B: 71, ALA B: 99, GLY B: 144, THR B: 145, GLY B: 146, ASP B: 179.
	3f	SER B: 178, LEU C: 248, GLY C: 350, PHE C: 351, VAL C: 353.
4YJ3	**3a**	VAL B: 177, LEU C: 248, PRO C: 325, ILE C: 355, VAL C: 353.
	3b	CYS B:12, GLU B: 71, ALA B: 99, ASN B: 101, GLY B: 144, THR B: 145, GLY B: 146, ASP B: 179, TYR B: 224.
	3c	GLY B: 11, CYS B: 12, TYR B: 224
	3d	VAL B: 177, VAL C: 250.
	3e	GLN B: 11, CYS B: 12, GLY B: 142, GLY B:143, TYR B: 224.
	3f	VAL B: 177, TYR B: 224, LYS C: 352.

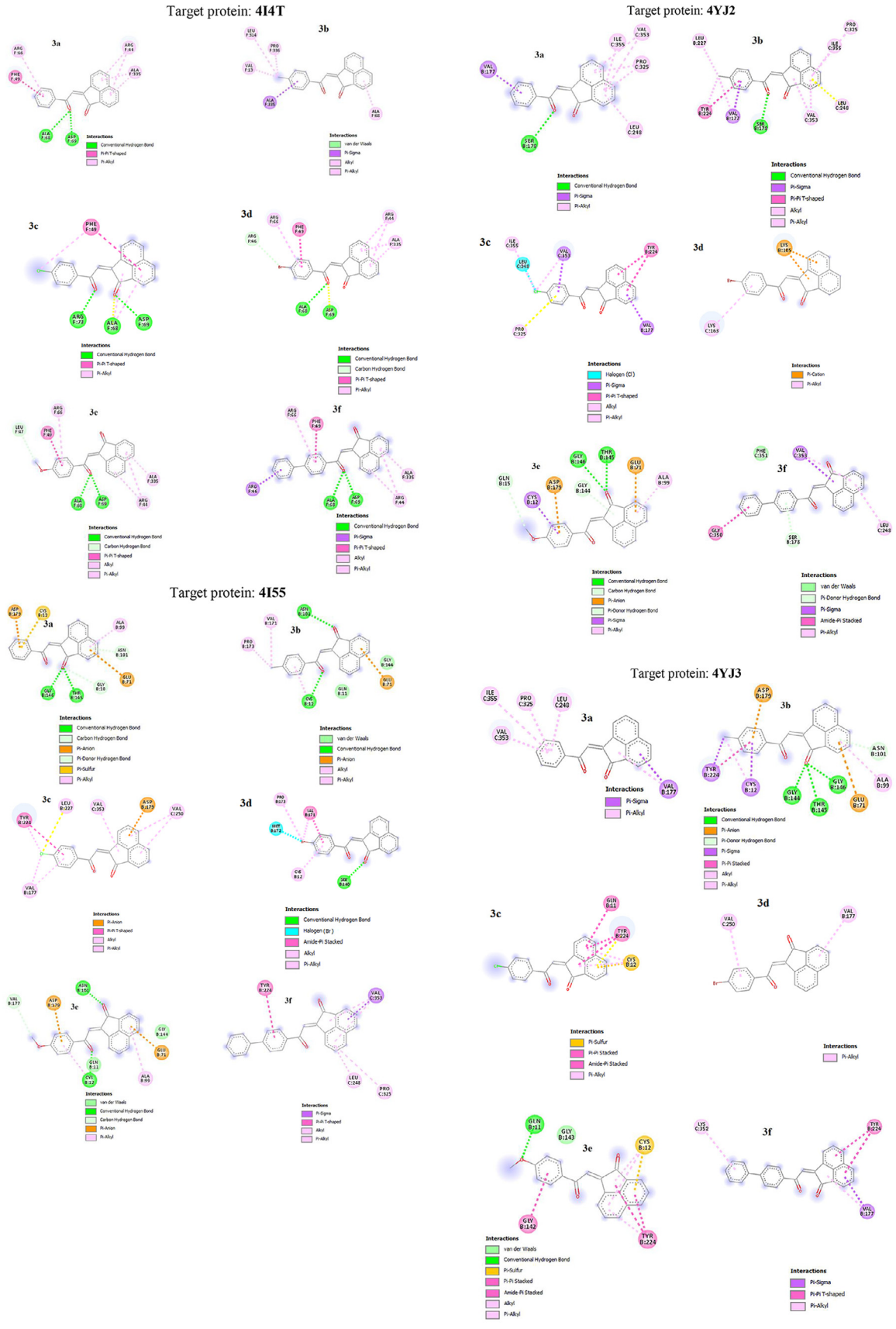


Fig 1. 2D diagram of acenaphthenone-2-ylidene ketones docked into the binding site of anti-cancer proteins.

Table 3
Prediction of in silico ADME properties of the acenaphthenone-2-ylidene ketones, **3a-f**.

Acenaphthenone-2-ylidene ketones	Molecular weight (g/mol)	Physicochemical parameters					Bioactivityscore
		Mi log P	TPSA (Å²)	No. of H-bond acceptor	No. of H-bond donor	No. of rotatable bonds	
3a	284.31	2.66	34.14	2	0	2	0.55
3b	298.33	2.59	34.14	2	0	2	0.55
3c	318.75	2.90	34.14	2	0	2	0.55
3d	363.20	3.01	34.14	2	0	2	0.55
3e	314.33	2.47	43.37	3	0	3	0.55
3f	360.40	3.31	34.14	2	0	3	0.55

format [31]. Before docking, the water molecules and other co-crystallized ligand molecules were removed from the target proteins and polar hydrogens were added using PyMoL software [32]. The active site of the protein was explained within the grid size 30Å × 30Å × 30Å in order to incorporate the residues of the active sites. The best fit conformation was analysed, which is based on the binding score, hydrogen bonding and other hydrophobic interactions. The binding interactions were visualized using Discovery studio visualizer. Affinity of best docked position of the molecule and protein target complex was determined by E-value (kcal/mol). It provides the prediction of binding free energy for docked molecule [21].

4I4T crystal structure of the tubulin-RB3-TTL-Zampanolide complex with binding energy (E) -9.20, -9.60, -8.80, -9.50, -9.30, -10.70 kcal/mol for **3a, 3b, 3c, 3d, 3e** and **3f** respectively. Organisms: Bos taurus, Rattus norvegicus, Gallus gallus. **4I55** Crystal structure of the tubulin-stathmin-TTL complex with binding energy (E) -9.00, -9.10, -7.80, -8.40, -8.40, -9.30 kcal/mol for **3a, 3b, 3c, 3d, 3e** and **3f** respectively. **4YJ2** Crystal structure of tubulin bound to MI-181 with binding energy (E) -8.60, -8.60, -8.80, -8.50, -8.70, -9.70 kcal/mol for **3a, 3b, 3c, 3d, 3e** and **3f** respectively. **4YJ3** crystal structure of tubulin bound with binding energy (E) -8.70, -8.80, -9.00, -8.10, -8.70, -9.40 kcal/mol for **3a, 3b, 3c, 3d, 3e** and **3f** respectively. From the above data, we can clear that 2-(2-(biphenyl-4-yl)-2-oxoethylidene)acenaphthylen-1(2H)-one (**3f**) shows good binding affinity to target proteins as shown in Fig 1. So, we can use **3f** as the best anticancer drugs in the acenaphthenone-2-ylidene ketones (**3a-f**) series. These acenaphthenone-2-ylidene ketones (**3a-f**) show good binding affinity to the target proteins than the binding affinity of the compounds to the same target proteins in a recently reported article [33].

By using Discovery studio visualizer, [34] we have to find the docking interaction of hydrogen bonds (classical and non-classical) and binding amino acid residues: alanine (ALA), asparagine (ASN), arginine (ARG), aspartic acid (ASP), cysteine (CYS), glutamine (GLN), glutamic acid (GLU), glycine (GLY), histidine (HIS), leucine (LEU), lysine (LYS), serine (SER), threonine (THR), tryptophan (TRP), tyrosine (TYR), valine (VAL) and phenylalanine (PHE) showed in the 2D interaction diagram (Fig 1).

4. In silico ADME property prediction

Computational simulation studies provide a quick and economic approach to determine the drug-like character of synthesized acenaphthenone-2-ylidene ketones, **3a-f**. SwissADME software was used to measure their bioactive score value of the prepared compounds. It was measured by estimating the different parameters Mi log P (partition coefficient), compound weight, heavy atoms, hydrogen donors, hydrogen acceptors and rotatable bonds Table 3.

Properties of absorption, distribution, metabolism, excretion and toxicity are included in In silico ADME and are exploited to predict the drug-likeness behaviour of the compounds based on Lipinski's rule of five [35–37]. According to Lipinski's rule, Mi log P values of compounds should be below 5, molecular weight is lower than 500, H-bond acceptors should be smaller than 10, H-bond donors should be lower than 5 and should have the bioactive score is smaller than one.

Mi Log P, is calculated by the methodology developed by Molinspiration [38] as a sum of fragment based contributions and correction factors. To determine the hydrophobic character of the synthesized compounds we are using the parameter Mi log P, which is necessary for analyzing the permeability skill of the compounds across the cell membrane. In the present study about the acenaphthenone-2-ylidene ketones **3a-f**, Mi log P values are found to be less than 5; it implies that the compounds should have appreciable penetrable talent across the central nervous system. The molecular weight of the synthesized compounds is less than 500. As per Lipinski regulation, these compounds have good drug-likeness criteria.

Here the number of H-acceptors is 2, 3 and the H-donor is zero for acenaphthenone-2-ylidene ketones, **3a-f**. Based on the Lipinski's rule of five, the compounds possess many H- acceptors and donors, they effectively interact with active sites. Topological molecular polar surface area (TPSA) is a commonly analyzed factor related to H-bonding (O and N atom counts) and is necessary to identify the cell permeability phenomena of **3a-f**. It is a significant parameter that was compared with the passive diffusion through the cell wall; hence, it agreed to pass the drug candidates inside the central nervous system. In the case of acenaphthenone-2-ylidene ketones **3a-f**, acquires TPSA values below 140 $Å^2$ and thereby possess good drug transport features and may be favoured for oral administration.

As per Lipinski's rule, molecule having higher number of rotatable bond, they become more stretchy and convenient for interface with the accurate active centre. Here the rotatable bonds are 2, 3 and have well-matched ability to interact with the living cells efficiently.

According to the Lipinski's rule, the compounds which possess bioactivity scores greater than 0 have excellent drug likeness proficiency [39]. In this case, acenaphthenone-2-ylidene ketones **3a-f**, have the bioactivity score is 0.55 and are scrutinized by measuring the activity score of GPCR (Human G-protein coupled receptors) ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor and enzyme inhibitor.

5. Conclusion

Acenaphthenone-2-ylidene ketones were independently synthesised and their propensity to undergo further transformations under conditions employed for Claisen-Schimidt reaction was examined. Geometry optimization using Gaussian, clearly revealed

that acenaphthenone-2-ylidene ketones have similar geometry, hence geometry has no role in controlling the Claisen-Schimidt reaction of acenaphthenone-2-ylidene ketones. Electromeric effects induced by substituents at the *para* position of the benzoyl group in the initially formed acenaphthenone-2-ylidene ketones may be responsible for the observed difference in their reactivity towards further transformations. Anticancer activity of the acenaphthenone-2-ylidene ketones were analysed (in silico) using AutoDock 4.2 Vina software. Drug likeness of the acenaphthenone-2-ylidene ketones were established using SwissADME software based on Lipinski's rule of five.

6. Experimental section

6.1. General methods

All reactions were conducted in oven-dried glassware. Reagents used were purchased from *Sigma Aldrich Chemical Co.* or *Spectrochem* and were used without further purification. Solvents used for experiments were distilled and dried according to procedures given in standard manuals. All reactions were monitored by thin layer chromatography (TLC). Analytical thin layer chromatography was performed on aluminium sheets coated with silica gel (*Spectrochem*); visualization was achieved by exposure to iodine vapours or UV radiation. Solvent removal was done on a *Heidolph* rotary evaporator. Gravity column chromatography was performed using 60-120 mesh silica gel (*Spectrochem*) and mixtures of hexane-ethyl acetate were used for elution. Melting points were recorded on a *Neolab* melting point apparatus. Infrared spectra were recorded using *JASCO FTIR 4100* spectrometer. NMR spectra were recorded a 400 MHz on a *Bruker* FT-NMR spectrometer. Chemical shifts are reported in δ (ppm) relative to TMS as the internal standard. Single Crystal XRD was done by *Bruker* XRD Instrument. Elemental analysis was performed using *Elementar Systeme (Vario EL III)*. Molecular mass was determined by fast atom bombardment (FAB) using *JMS 600 JEOL* mass spectrometer. Unless otherwise mentioned, all commercially available solvents and reagents were used as received and reactions were performed under normal conditions. Characterization data for **4a-c, 5a-c** and **6a-c** are available in earlier publications from our group [17,18].

6.2. Common procedure for the synthesis of acenaphthenone-2-ylidene ketones (3a-f) by Wittig's reaction

Para substituted acetophenones (**7a-f**, 25 mmol) was slowly added to a chloroform solution (6 mL) of triphenylphosphine (25 mmol) and the solution was filtered into anhydrous ether (1 Litre). The precipitate formed was filtered, collected and dried. The product formed was recrystallized from water in the form of white powder (**8a-f**, 60-68%).

A mixture of corresponding triphenylphosphonium bromide (**8a-f**, 7.0 g) and 10% aqueous sodium carbonate (250 mL) was well mixed for 15h. The mixture was filtered and insoluble portion was taken up in hot benzene (200 mL). Some unreacted bromide was removed by filtration; addition of petroleum ether to the benzene filtrate afforded the compound **9a-f** (58-65%) as white powder.

A solution of acenapthenequinone (**1**, 27 mmol) and triphenylphosphinebenzoylmethylene (**9a-f**, 27 mmol) in ethanol (30 mL) was stirred at room temperature for 2h. The product was separated, filtered and purified by recrystallization from ethanol-chloroform (1:3) mixture to give acenaphthenone-2-ylidene ketones **3a-f** (57-68%).

2-(2-oxo-2-phenylethylidene)acenaphthylen-1(2H)-one (3a) [17,18,40]**:** Yellow needles, Yield: 3.18 g (60%), mp: 108-110°C, IR ν_{max} (KBr): 1722, 1671 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$): δ 8.97-7.26 (12H, m, aromatic and vinylic protons), ^{13}C NMR ($CDCl_3$): δ 200.32, 199.21, 141.13, 140.84, 138.10, 134.86, 133.25, 131.02, 130.87, 130.38, 129.23, 128.40, 128.33, 127.62, 126.12, 123.19, 118.29,96.43. MS (FAB): m/z 284 (M^+), 105 Elemental analysis calculated for $C_{20}H_{12}O_2$: C 84.49, H 4.25. Found: C 84.43, H 4.39.

2-(2-oxo-2-p-tolylethylidene)acenaphthylen-1(2H)-one (3b) [17,18,40]**:** Yellow needles, Yield: 3.39 g (64%), mp: 143-145°C, IR ν_{max} (KBr): 1710, 1674 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$): δ 8.97-7.21 (11H, m, aromatic and vinylic protons), 2.40 (3H, singlet, methyl protons) ^{13}C NMR ($CDCl_3$): δ 200.16, 199.34, 153.81, 144.29, 134.93, 134.47, 132.01, 131.34, 131.34, 130.31, 129.80, 129.51, 129.51, 129.64, 127.50, 127.17, 126.81, 122.52, 25.80. MS (FAB): m/z 295 (M^+), 119. Elemental analysis calculated for $C_{21}H_{14}O_2$: C 84.54, H 4.74. Found: C 84.48, H 4.76.

2-(2-(4-chlorophenyl)-2-oxoethylidene)acenaphthylen-1(2H)-one (3c) [17,18,40]**:** Yellow needles, Yield: 3.60 g (68%), mp: 187-189°C, IR ν_{max} (KBr): 1716, 1668 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$): δ 8.81-7.14 (11H, m, aromatic and vinylic protons), ^{13}C NMR ($CDCl_3$): δ 200.4, 194.21, 140.93, 140.14, 139.10, 134.99, 132.05, 131.54, 130.77, 130.18, 129.08, 128.45, 128.39, 127.92, 126.85, 122.09, 117.99, 96.19. MS (FAB): m/z 318 (M^+), 139. Elemental analysis calculated for $C_{20}H_{11}ClO_2$: C 75.36, H 3.48. Found: C 75.39, H 3.41.

2-(2-(4-bromophenyl)-2-oxoethylidene)acenaphthylen-1(2H)-one (3d) [17,18,40]**:** Yellow needles, 2.62 g (57%), mp: 197-199°C, IR ν_{max} (KBr): 1710, 1663 cm^{-1} (C=O), ^{1}H NMR ($CDC1_3$): δ 8.80-7.12 (11H, m, aromatic and vinylic protons), MS (FAB): m/z 362 (M^+), 183. Elemental analysis calculated for $C_{20}H_{11}BrO_2$: C 66.14, H 3.05. Found: C 66.18, H 3.11.

2-(2-(4-methoxyphenyl)-2-oxoethylidene)acenaphthylen-1(2H)-one (3e) [17,18,40]**:** Yield: 2.90 g (63%), mp: 161-163°C, IR ν_{max} (KBr): 1722, 1670 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$): δ 8.84-6.91 (11H, m, aromatic and vinylic protons), 3.88 (3H, singlet, methoxy protons), ^{13}C NMR ($CDCl_3$): δ 193.66, 189.13, 164.04, 140.70, 138.22, 132.62, 131.31, 131.24, 130.80, 130.47, 129.84, 129.12, 128.37, 121.93, 117.69, 115.41, 114.62, 114.13, 113.98, 113.05, 110.99, 108.72, 107.71, 106.09, 104.37, 96.22, 55.40. MS (FAB): m/z 314 (M^+), 135. Elemental analysis calculated for $C_{21}H_{14}O_3$: C 84.54; H 4.73. Found: C 84.50, H 4.69.

2-(2-(biphenyl-4-yl)-2-oxoethylidene)acenaphthylen-1(2H)-one (3f) [17,18,40]**:** Yield: 2.76 g (60%), mp: 187-189°C, IR ν_{max} (KBr): 1715, 1650 cm^{-1} (C=O), ^{1}H NMR ($CDCl_3$) δ 8.78-7.25 (16H, m, aromatic and vinylic protons), ^{13}C NMR ($CDCl_3$) δ 201.89, 194.87, 146.41, 140.11, 135.31, 132.47, 132.37, 131.43, 130.81, 129.47, 128.94, 128.83, 128.39, 128.23, 127.79, 127.40, 127.14, 126.69, 126.48, 124.04, 122.04, 117.87, 112.89, 109.54, 108.14, 96.22. MS (FAB): m/z 360 (M^+), 181. Elemental analysis calculated for $C_{26}H_{16}O_2$: C 86.64, H 4.47. Found: C 86.68; H 4.42.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2020.129209.

CRediT authorship contribution statement

Daly Kuriakose: Software, Formal analysis, Investigation, Data curation, Writing - original draft. **Roshini K. Thumpakara:** Investigation, Writing - original draft, Data curation, Formal analysis. **Jesna A:** Visualization, Investigation. **Jomon P. Jacob:** Conceptualization, Methodology, Supervision.

References

[1] M.R. Jayapal, K.S. Prasad, N.Y. Sreedhar, Synthesis and characterization of 2,6-dihydroxy substituted chalcones using PEG-400 as a recyclable solvent, J. Pharm. Sci. Res. 2 (2010) 450–458.

[2] A.F.M. Rahman, R. Ali, Y. Jahng, A.A Kadi, A facile solvent free claisen-schmidt reaction: synthesis of α,α'-bis-(Substituted-benzylidene)cycloalkanones and α,α'-bis-(Substituted-alkylidene)cycloalkanones, Molecules 17 (2012) 571–583.

[3] A. Rayar, M.S. Iyarreta Veitía, C. Ferroud, An efficient and selective microwave-assisted Claisen-Schmidt reaction for the synthesis of functionalized benzalacetones, SpringerPlus 4 (2015) 221.

[4] R. Pal, Ammonium chloride catalyzed microwave-assisted ClaisenSchmidt reaction between ketones and aldehydes under solvent free conditions, IOSR J. App. Chem. 3 (2013) 74–80.

[5] M.R. Mousavi, M.T. Maghsoodlou, H. Gharari, Sodium carbonate-catalyzed Claisen–Schmidt condensation: one-pot synthesis of highly functionalized cyclohexenones under environmental conditions, Res. Chem. Intermed. 42 (2016) 2233–2246.

[6] D. Ispán, E. Szánti-Pintér, M. Papp, J. Wouters, N. Tumanov, B. Zsirka, Á. Gömöry, L. Kollár, R. Skoda-Földes, The use of switchable polarity solvents for the synthesis of 16-Arylidene steroids via claisen–schmidt condensation, Eur. J. Org. Chem (2018) 3236–3244 2018.

[7] X. Qi, X. Yan, W. Peng, J. Zhang, Y. Tong, J. Li, D. Sun, G. Huid, J. Zhang, Graphene-induced hierarchical mesoporous MgO for the Claisen–Schmidt condensation reaction, New J. Chem. 43 (2019) 4698–4705.

[8] D. Kumar, J.S.Sandhu Suresh, An efficient green protocol for the synthesis of chalcones by a Claisen–Schmidt reaction using bismuth(III)chloride as a catalyst under solvent-free condition, Green Chem. Lett. Rev. 3 (2010) 283–286.

[9] R. L.Reeves, Wiley-Intersciences, New York, NY, USA, 1966, pp. 580–600.

[10] T. Mukaiyama, in: W.G. Dauben (Ed.), Organic Reactions, 28, J. Wiley & Sons, New York, NY, USA, 1982, pp. 203–331.

[11] A.T. NieIsen, W.J. Houlihan, in: R. Adams, A.H. Blatt, V. Boekelheide, T.L. Cairns, D.J. Cram, H.O. House (Eds.), Organic Reactions. In The Aldol Condensation, 16, J. Wiley & Sons, New York, NY, USA, 1968, pp. 1–438.

[12] Q.H. Fan, Y.M. Li, A.S.C. Chan, Recoverable catalysts for asymmetric organic synthesis, Chem. Rev. 102 (2002) 3385–3466.

[13] T. Narender, K.P. Reddy, A simple and highly efficient method for the synthesis of chalcones by using borontrifluoride-etherate, Tetrahedron Lett. 48 (2007) 3177–3180.

[14] S. Muthadi, B. Macha, P. Mamidi, S. Manchinella, A. Garlapati, R.R. Akkinepalli, Synthesis and evaluation of new brominated azaflavones and azaflavanone derivatives as cytotoxic agents against breast cancer cell line (MCF-7), Indian J. Pharm. Educ. 53 (2019) 117–126.

[15] T.P. Robinson, R.B. Hubbard, T.J. Ehlers, J.L. Arbiser, D.J. Goldsmith, J.P. Bowen, Synthesis and biological evaluation of aromatic enones related to curcumin, Bioorg. Med. Chem 13 (2005) 4007–4013.

[16] A.T. Nielsen, W.J. Houliban, The aldol condensation, Organ. React. 16 (1968) 1438.

[17] J.J. Vadakkan, V. Raman, N.B. Fernandez, S. Prathapan, B. Jose, A novel solvent-assisted domino Michael-aldol reaction of acenaphthenequinone with acetophenones, New J. Chem 27 (2003) 239–241.

[18] J.P. Jacob, C. Kunjachan, L.U. Sajitha, R.K. Thumpakara, K. Rakesh, V. Nidhisha, P.A. Unnikrishnan, S. Prathapan, Domino reaction sequences leading to the formation of 2:2 adducts between acenaphthenequinone and acetophenone, ARKIVOC (2014) 127–138 vi.

[19] O. Trott, A.J. Olson, Software news and update autodock vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J. Comput. Chem. 31 (2010) 455–461.

[20] S. Dallakyan, A.J. Olson, in: Chemical Biology: Methods Protocols, Humana Press, New York, 2015, pp. 243–250.

[21] G.M. Morris, D.S. Goodsell, R.S. Halliday, R. Huey, W.E. Hart, R.K. Belew, A.J. Olson, Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function, J. Comput. Chem. 19 (1998) 1639–1662.

[22] L.U. Sajitha, M. Sithambaresan, J.P. Jacob, M.R.P. Kurup, Crystal structure of (4-chlorophenyl)[2-(10-hydroxyphenanthren-9-yl)phenanthro[9,10-b]furan-3-yl]methanone, Acta Cryst. E70 (2014) 355–358.

[23] J.P. Jacob, M. Sithambaresan, C. Kunjachan, M.R.P. Kurup, Crystal structure of 8-[7,8-bis(4-chlorobenzoyl)-7H-cyclopenta[a]acenaphthylen-9-yl]naphthalene-1-carboxylic acid, Acta Cryst. E71 (2015) 38–41.

[24] M. Hassan, Z. Ashraf, Q. Abbas, H. Raza, S.-Y. Seo, Exploration of novel human tyrosinase inhibitors by molecular modeling, docking and simulation studies, Interdiscip. Sci. 10 (2018) 68–80.

[25] A. Tan, S. Kizilkaya, U. Kelestemur, A. Akdemir, Y. Kara, The synthesis, anticancer activity, structure-activity relationships and molecular modelling studies of novel isoindole-1,3(2H)-dione compounds containing different functional groups, Anticancer Agents Med. Chem (2020), doi:10.2174/1871520620666200410080648.

[26] P. Bansode, P. Patil, P. Choudhari, M. Bhatia, A. Birajdar, I. Somasundaram, G. Rashinkar, Anticancer activity and molecular docking studies of ferrocene tethered ionic liquids, 290 (2019) 111182.

[27] S. Tahlan, S. Kumar, K. Ramasamy, S.M. Lim, S.A.A. Shah, V. Mani, B. Narasimhan, In-silico molecular design of heterocyclic benzimidazole scafolds as prospective anticancer agents, BMC Chemistry 13 (2019) 90.

[28] Z. Luo, A. Valeru, S. Penjarla, B. Liu, I. Khan, Synthesis, anticancer activity and molecular docking studies of novel pyrido[1,2-a]pyrimidin-4-one derivatives, Synth. Commun. 49 (2019) 2235–2243.

[29] Y.-L. Zhang, R. Yang, L.-Y. Xia, R.-J. Man, Y.-C. Chu, A.-Q. Jiang, Z.-C. Wang, H.-L. Zhu, Synthesis, anticancer activity and molecular docking studies on 1,2-diarylbenzimidazole analogues as anti-tubulin agents, Bioorg. Chem. 92 (2019) 103219.

[30] S.R. Shah, K.D. Katariya, D. Reddy, Quinoline-1,3-Oxazole hybrids: syntheses, anticancer activity and molecular docking studies, Chem. Select 5 (2020) 1097–1102.

[31] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne, The protein data bank, Nucl. Acids Res. 28 (2000) 235–242.

[32] The PyMOL Molecular Graphics System, Version 1.5.0.4 Schrodinger LLC.

[33] A. Viji, V. Balachandran, S. Babiyana, B. Narayana, V.V. Saliyan, Molecular docking and quantum chemical calculations of 4-methoxy-{2-[3-(4-chlorophenyl)-5-(4-(propane-2-yl) phenyl)-4, 5-dihydro-1H-pyrazol-1-yl]- 1, 3-thiazol-4-yl}phenol, J. Mol. Struct. 1203 (2020) 127452.

[34] Discovery Studio 4.5 Guide, Accelrys Inc., San Diego, 2009. http://www.accelrys.com.

[35] C.A. Lipinski, Lead- and drug-like compounds: the rule-of-five revolution, Drug Discov. Today Technol. 1 (2004) 337–341.

[36] S. Singh, A.K. Gupta, A. Verma, Molecular properties and bioactivity score of the aloe vera antioxidant compounds – in order to lead finding, RJPBCS 4 (2013) 876–881.

[37] S.S.A. Fathima, M.M.S. Meeran, E.R. Nagarajan, Synthesis of novel (E)-2-((anthracen-9-ylmethylene)amino)pyridin-3-ol and its transition metal complexes: multispectral characterization, biological evaluation and computational studies, J. Mol. Liq 279 (2019) 177–189.

[38] Molinspiration Cheminformatics [Homepage on the Internet], Nova Ulica, Slovensky Grob, Slovakia, (2012); http://www.molinspiration.com/.

[39] J. Lakshmipraba, S. Arunachalam, R.V. Solomon, P. Venuvanalingam, A. Riyasdeen, R. Dhivya, M.A. Akbarsha, Surfactant–copper(II) Schiff base complexes: synthesis, structural investigation, DNA interaction, docking studies, and cytotoxic activity, J. Biomol. Struct. Dyn. 33 (2015) 877–891.

[40] R.K. Thumpakara, Ph. D Thesis, CUSAT, 2007.